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Chronic Cough and Sinusitis in Children

— The Role of Antimicrobials —

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We evaluated the role of antimicrobials in the treatment of chronic maxillary sinusitis in children with chronic cough. At the first visit 216 of 276 cases with chronic cough had radiologically abnormal maxillary sinuses (78.3%). By the Waters x-rays around 50 cases each were assigned randomly to four groups; among them, 48 cases were given an amoxicillin, 51 cases were given trimethoprim-sulfamethoxazole (TMS), 53 cases were given amoxicillin plus TMS and 50 cases were given expectorant plus decongestant (control) group. Thus, 202 children were included for data analysis. Treatment was given for two weeks in each group. The group treated with antimicrobials had a significantly higher cure rate than that of expectorant plus decongestant group ($P<0.001$). Most of the patients who had roentgenographic improvement have successfully recovered from the chronic cough and the other cardinal signs of chronic sinusitis.

Key Words: Chronic cough, Chronic sinusitis, Antimicrobials.

Pediatricians often encounter cases having chronic cough lasting for several weeks to months. Cough itself is not an illness but a symptom of an underlying stimulus or disease; therefore, evaluation and treatment of cough should be directed at the underlying illness rather than at the cough itself. The causes of chronic cough vary (Eigen, 1982). Chronic bronchitis is the most common working diagnosis when a pediatrician sees cases with chronic cough lasting more than two weeks (Taussing *et al.*, 1981). According to national statistics (Wilder, 1970), more than 2.5 million children in the United States were supposed to have chronic bronchitis. Cough has also been recognized as a manifestation of airway hyperreactivity in children (Cloutier and Loughlin, 1981). Sinusitis, particularly in older children and paranasal sinusitis is part of the cold process due to the fact that the continuity of the nasal and sinus membranes would seem to favor a simultaneous inflammatory response when a viral infection or offending allergen is present (Wald et al., 1981). Since postnasal drip is one of the important causes of a chronic cough (Eigen, 1982) and the authors have seen postnasal drip in many cases with chronic cough lasting more than three weeks, this study was conducted to find out: (1) whethe chronic cough could be correlated with chronic maxillary sinusitis; (2) whether sinusitis should be treated or not with appropriate anti-

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microbials; (3) whether chronic cough could be controlled by treating the sinusitis.

MATERIALS AND METHODS

Two hundred and seventy-six children between 3 and 15 years of age, seen at the outpatient department, Severance Hospital, Yonsei University College of Medicine, with chronic cough lasting more than three weeks (ranging from 22 days to six months), were studied consecutively and prospectively. Two hundred and sixteen cases were selected for study if a Waters view demonstrated haziness of one or both maxillary sinuses or if there was more than 6mm of mucosal thickening of one or both maxillary sinuses. Specific diseases with chronic cough such as whooping cough, bronchial asthma, pulmonary tuberculosis, pneumonia, pleurisy, empyema and allergic cough were all excluded. In order to rule out the above diseases, PPD skin test, chest x-ray, complete blood counts, total eosinophile count, careful allergy history and epinephrin test were routinely carried out as well as careful examination of the characteristic clinical findings.

For each child information was obtained concerning the presence and duration of cough, headache, sore throat, throat clearing, postnasal drip, rhinorrhea and nasal stuffiness. X-ray films were read by a competent pediatric radiologist, who was not aware of the clinical findings or treatment. The interpretations were classified as follows: (1) normal, (2) complete haziness, one or both sides, and (3) showing mucosal thickening (<6mm), on one or both sides. Mucosal thickening of the maxillary antral wall was determined by measurement of the nearest distance from the airmucosal interface to the most lateral part of the sinus wall. The patients with retention cysts or polyps on initial x-rays were excluded from this study. IgG levels were measured by the radial immunodiffusion test by using N-Partigen (Behring) and IgE by the paper radioimmunosolvent test (Pharmacia Diagnostics), and the results were compared with the data of Cejka et al. (1974) and of Kjellman et al. (1976) respectively.

After informed consent was obtained from the parents, patients were randomly assigned to either an antimicrobial group: (1) anoxicillin group, (2) trimethoprim-sulfamethoxazole (TMS) group and (3) amoxicillin plus TMS group or to an (4) expectorant plus decongestant group (control) successively irrespective of x-ray findings. Expectorants (S-Carboxymethyl cyctine, Bromhexine hydrochloride, Potassium chloride etc.) and decongestants (0.25% Phenylephrine hydrochloride nose drops and ephedrine orally) were given to all the control group for easier drainage (dose dependent on weight). Amoxicillin (50mg/Kg/day) was administered every 8 hrs and TMS 30mg/Kg/day) was administered every 12 hrs. Patients continued the treatment for 14 days unless their condition worsened after 5 days of treatment or unless they had side effects from their medications. If this occurred, they were excluded from the study. In our opinion, a placebo treatment was not justified because expectorant and decongestant treatment served as a control for the antimicrobial regimens.

After 14 days of therapy the patients were questioned regarding symptoms, and reexamined. The Waters radiograph was repeated and the following decisions were made: (1) If there was no change in x-ray and in symptoms, this was interpreted as being unchanged or worse. (2) If patients responded clinically, these were interpreted either as normal (no cough) or marked improvement (cough a few times a day) or moderate improvement (cough, less than half of initial visit) and if there was improvement radiologically, decrease in mucosal thickening

or loss of opacification, it was interpreted as partial clearing or complete clearing respectively. In cases of complete clearing, the treatment regimen was discontinued and participation in the study ended. In cases of partial clearing, the same treatment was continued for another two weeks to see if there would be further clearing, however, the results were not included in this report.

Treatments were compared statistically using chi square analysis to assess statistical significance. In the analysis of the association between the results from the Waters view changes and presenting symptoms and signs of the patients, X^2 test and correlation of the attributes were computed.

RESULTS

Between January 1981 and December 1982, 276 cases of chronic cough lasting more than three weeks and ranging from 22 days to months, were studied; 216 cases were found to have radiologic evidence of maxillary sinusitis. The infection rate was 78.3 per cent. In the amoxicillin group 48 cases were followed, 51 cases were followed up in the TMS group, 53 cases were followed up in the amoxicillin plus TMS group and 50 cases were followed up in the expectorant plus decongestant group. Thus, 202 children were included for data analysis. There were 124 boys and 78 girls, with an age range of 3 to 15yr (table 1). The mean duration of cough with other respiratory symptoms requiring our consultation was 8 weeks (±4 S.D.). Symptoms and signs on initial presentation are seen in tabe 2. Cough, nasal stuffiness, rhinorrhea, headache and sore throat were commonly seen in those with marked x-ray changes. The presence of postnasal drip and tenderness of the paranasal sinus region was observed in the majority

Table 1. Age and sex distribution of 202 cases showing abnormal maxillary sinuses by Waters view

Age	Male	Female	Total	%
3-6	36	11	47	23.3
6-10	64	53	117	57.9
10-15	24	14	38	18.8
Total	124	78	202	100.0

Table 2. Presenting symptoms and signs of 202 patients with abnormal maxillary sinus radiographs

Symptoms and signs	Number of cases	%
Symptoms		
Cough	202	100.0
Nasal stuffiness	139	69.0
Rhinorrhea	121	59.8
Headache	84	41.7
Sore throat	65	32.1
Signs		
Postnasal drip	106	52.4
Tenderness on PNS* region	98	48.7
Tonsillar enlargement	77	38.0

* PNS : Paranasal sinus

of patients with sinus cavities that were opacified. Initial x-ray evaluation of the maxillary sinus cavities (Table 3) revealed 119 with haziness of one (24) or both (95) sinus cavities, and 83 with greater than 6mm of mucosal thickening in one (30) or both (53) sinus cavities. IgG level was measured in all 202 cases, none of the cases showed immune deficiency. IgE level was also measured in all 202 cases and 10 of them were found to have high IgE level. Two of them responded to amoxicillin well, 2 of them responded to TMS and two of them responded to amoxicillin plus TMS well. One did not respond to amoxicillin, one did not respond to TMS and two of them did not respond to expectorant plus decongestant at all.

As shown in table 3, treatment with

Table 3. Initial Waters view findings and maxillary changes at the 2 weeks follow up in both antimicrobial group and expectorant plus decongestant group

Water view findings at initial evaluation		Results of treatment at 2 weeks		
		Complete clearing	Partial clearing	Same or worse
Antimicrobial group				
Amoxicillin				
Haziness	28	12	8	8
Both side	22	10	4	8
Right side	4	2	2	0
Left side	2	0	2	0
Mucosal thickening	20	4	6	10
Both side	12	2	4	6
Right side	4	0	2	2
Left side	4	2	0	2
TMS*				
Haziness	30	15	8	7
Both side	24	13	6	5
Right side	3	1	1	1
Left side	3	1	1	1
Mucosal thickening	21	5	11	5
Both side	13	3	7	3
Right side	5	2	2	1
Left side	3	0	2	1
Amoxicillin + TMS				
Haziness	31	14	10	7
Both side	25	11	8	6
Right side	3	2	1	0
Left side	3	1	1	1
Mucosal thickening	22	5	12	5
Both side	15	3	9	3
Right side	4	1	2	1
Left side	3	1	1	1
Expectorant + decongestant group				
Haziness	30	6	4	20
Both side	24	4	3	17
Right side	3	1	0	2
Left side	3	1	1	1
Mucosal thickening	20	3	4	13
Both side	13	2	2	9
Right side	4	0	1	3
Left side	3	1	1	1

* TMS: Trimethoprim-sulfamethoxazole

Antimicrobial versus expectorant plus decongestant group: $X^2=23.759$

df= 2, $P<0.001$

Table 4. Outcome of initial treatment with antimicrobials and expectorants in both maxillary changes and improvement of symptoms and signs

Treatment group	Waters view changes		Presenting symptoms and signs			
			Normal	Marked improvement	Moderate improvement	No change
Antimicrobial group	Complete clearing	55	42	8	5	0
	Partial clearing	55	6	22	27	0
	Same or worse	42	0	0	0	42
Expectorant and decongestant group	Complete clearing	9	6	2	1	0
	Partial clearing	8	1	4	3	0
	Same or worse	33	0	0	0	33

Antimicrobial group: $X^2=228.12$, df=4, $P<0.001$, correlation of attribute =0.866; Expectorant plus decongestant group: correlation of attribute=0.799.

amoxicillin resulted in 30 improvements and 18 failures (30 of 48, cure rate 62.5%); treatment with TMS resulted in 39 improvements and 12 failures (39 of 51, cure rate 76.5%); treatment with amoxicillin plus TMS resulted in 41 improvements and 12 failures (41 of 53, cure rate 77.4%), thus in the total antimibrobial group, the cure rate was 72.4 per cent (110 of 152); and treatment with expectorants and decongestants resulted in 17 improvements and 33 failures (17 of 50, cure rate 34.0%). The difference between the antimibrobial group and expectorant plus decongestant group in cure rate was statistically significant ($P<0.001$). However, in comparing the cure rate among the amoxicillin, TMS and amoxicillin plus TMS there seemed to be little difference ($P>0.05$), although the amoxicillin group showed a poorer cure rate. There was a tendency that complete clearing after 2 weeks treatment was more often seen in those cases with opacification at the time of the initial Waters view, while there was only partial clearing in those cases with mucosal thickening, but the difference was not statistically significant in all the groups ($P>0.05$).

According to table 4, maxillary sinus changes after 2 weeks of treatment irrespective of the treatment group had a close relationship to the improvement of symptoms and signs. If the Waters view changed to complete clearing, the majority of cases became normal or markedly improved; if Waters view changed to partial clearing, the majority of cases showed marked or moderate improvement; and if the Waters view was unchanged or worse, the symptoms and signs did not show any change. All the subjects who responded to the above regimens reported a diminution of their respiratory symptoms, especially cough, nasal stuffiness, headache and postnasal drip. The relationship was statistically highly correlated.

DISCUSSION

Upper respiratory tract infection is known to be the most frequent of all pediatric illnesses. This usually means an acute viral infection of the nasopharynx and sinuses associated with mild, if any, constitutional symptoms (Wald *et al.*, 1981; Aifaro, 1962). The age of greatest incidence of upper respiratory tract infections was from the latter part of the first year of life to 6 or 7 years. During this time it could be expected that the average child would have 3 to 6 "colds" a year. In chronic cough, the child seems to recover from one acute attack only to enter another, or there is more or less persistent rhinitis and cough (Boat *et al.*, 1979).

The reliability of radiographic evaluation in sinusitis as a diagnostic tool has been repeatedly demonstrated (Cloutier and Loughlin, 1981; Wald *et al.*, 1981; Alfaro, 1962). Radiologic examination was found to be valuable both in assessing the initial extent of involvement and in following the response to therapy (Evans *et al.*, 1975; Kogutt and Swischuk, 1973). For these reasons, the authors have decided to use Waters view for evaluation of maxillary sinuses for both the initial visit and follow-up study. Factors that prevent or obstruct the drainage of respiratory secretions were probably important in determining the likelihood of bacterial superinfection. The openings or ostia of each sinus differ in size and configuration. These differences contributed to the relative susceptibility of each sinus to inflammatory and infectious processes (Wald *et al.*, 1981). Completely opaque sinuses had free fluid or pus by aspiration in 80 to 88 per cent of the patients (McNeill, 1963; Axelsson *et al.*, 1970; Vusrinen *et al.*, 1962). In chronic maxillary sinusitis, the most frequent radiologic finding was thickening of the mucous membrane; retention cysts and polyps were occasionally seen (Wald *et al.*, 1981). In this study, total haziness was seen in 58.9 per cent, and mucosal thickening was seen in 41.1 per cent of the 202 chronic cough cases, and we found that 216 cases out of 276 with chronic cough had an abnormal maxillary sinus by the Waters view. The infection rate was 78.3 per cent. This was a far higher infection rate as compared with the data (Rachelefsky *et al.*, 1978) on respiratory allergy cases.

Our study is the first to evaluate whether or not antimicrobial agents can affect the radiologically abnormal maxillary sinus in children with chronic cough. On the basis of our findings (despite the lack of sinus cultures), it appears that a majority of our patients most likely harbor bacterial organisms within radiologically abnormal maxillary sinuses. Prior studies (Evans *et al.*, 1975; Hamory *et al.*, 1979; Axelsson and Chidekel, 1972) in adults have demonstrated that the presence of an opacified maxillary sinus or one with more than 6mm of thickening is usually a bacterially infected sinus. The response to amoxicillin and TMS suggest that H. influenzae is the predominant organism, even in children older than 6 yrs of age. From our data it is not possible to evaluate the role of anaerobes, although the majority of anaerobes removed from the sinuses in prior studies were penicillin sensitive (Evans *et al.*, 1975).

The bacteriology of sinus disease has been studied in both adults and children. Normal sinuses do not yield bacteria (Bjorkwall, 1950) and nasally obtained specimens are believed to be of little diagnostic value because of contamination. Cultures obtained directly from sinus cavities in children with acute disease have yielded S. pneumoniae, H. influenzae, and Branhamella catarrhalis (Wald *et al.*, 1981), although up to 40 per cent of these have negative cultures (Nylen *et al.*, 1972; Axelsson and Bror-

son, 1973). Cultures obtained directly from the sinus cavities in adults (Evans *et al.*, 1975) with acute disease most commonly grew H. influenzae, S. pneumoniae, Streptococcus viridans, and S. aureus. Chronic sinus disease (more than 1 yr) (Frederick and Braude, 1974) frequently yields anaerobes (alpha streptococci, Bacteroides, Vellonella, and Corynebacterium). Anaerobic organisms were not recovered from the maxillary sinuses of 30 children with acute sinusitis (Wald *et al.*, 1981); anaerobes in chronic sinusitis in childhood have not been adequately evaluated. Many authors believe that S. aureus is a frequent contaminant and not a cause of sinus disease.

We would have preferred correlating our findings with direct sinus cultures. However, the authors did not feel that the procedure was justified in children, unless intensive medical therapy had failed. Nasopharyngeal cultures were obtained in this study, but the results were withheld from the report because of prior evidence demonstrating poor correlation of such cultures with the organisms obtained directly from the sinus cavity.

The diagnostic role of ultrasonography needs to be further explored. It was not helpful when evaluating young children with acute sinusitis (Wald *et al.*, 1981). However, ultrasonic findings correlated (90%) with the results of sinus irrigation in adults and older children (Mann *et al.*, 1977; Revonta, 1979). Transillumination appears to be of no benefit in diagnosing sinusitis in adults (Spector *et al.*, 1981), but this procedure has not been fully evaluated in children. The effectiveness of expectorants and decongestants applied topically or administered by mouth in patients with chronic infection has not been adequately studied. In this study, 17 of 50 (34.0%) cases had radiologic evidence of improvement as well as clinical improvement. Limited investigation of specific agents in clinical rhinitis have shown that some produce a decrease in nasal resistance (Aschan, 1974; Roth *et al.*, 1977).

In this study, TMS and, to a lesser extent, amoxicillin were effective in reversing the radiologically abnormal maxillary sinus and improving clinical symptoms and signs. Rechelefsky *et al.* (1982) have observed that amoxicillin was more effective than TMS in treating chronic sinusitis in children with respiratory-allergy. Chronic symptoms, notably cough and nasal stuffiness and discharge, improved and bronchospasm was more readily controlled. The antimicrobial treatment group had a significant higher cure rate as compared with that of the control expectorant and decongestant group. It was also found that most of the patients who had radiologic improvement have successfully recovered from the chronic cough and the other cardinal signs of chronic sinusitis.

From this study, it is suggested that chronic sinusitis could be a contributing factor in chronic cough of unknown cause. Therefore, any children with chronic cough of unknown etiology lasting more than 3 weeks, should have radiologic evaluation for possible sinusitis. Antimicrobial treatment preferably with amoxicillin or TMS is indicated when the radiograph reveals haziness, or a mucosal wall greater than 6mm thick. Antimicrobials should be administered for at least 14 days. Patients who have continuing significant symptoms with unchanged radiographs after 14 days of treatment should be referred to an ENT specialist for consideration of antral puncture and lavage. The problem of sinusitis and chronic cough needs to be further explored.

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